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Atsuro NAKAZATO, et al.

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For: THIENOPYRIMIDINE AND THIENOPYRIDINE DERIVATIVES SUBSTITUTED WITH CYCLIC AMINO GROUP

SUBMISSION OF PRIORITY DOCUMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Submitted herewith is a certified copy of the priority document on which a claim to priority was made under 35 U.S.C. § 119. The Examiner is respectfully requested to acknowledge receipt of said priority document.

Respectfully submitted,

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This is to certify that the annexed is a true copy of the following application as filed with this Office.

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Applicant(s): 大正製薬株式会社

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[TITLE OF INVENTION]

THIENOPYRIMIDINE AND THIENOPYRIDINE DERIVATIVES SUBSTITUTED WITH CYCLIC AMINO GROUP

[DETAILED DESCRIPTION OF THE INVENTION]

[TECHNICAL FIELD]

The present invention relates to a therapeutic agent for diseases in which corticotropin releasing factor (CRF) is considered to be involved, such as depression, anxicty, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastral diseases, drug dependence, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseasesalpecia, irritable bowel syndrome, sleep disorders, epilepsy, dermatitides, schizophrenia, etc.

[DESCRIPTION OF THE PRIOR ART]

CRF is a hormone comprising 41 amino acids (Science, 213, 1394-1397, 1981; and J. Neurosci., 7, 88-100, 1987), and it is suggested that CRF plays a core role in biological reactions against stresses (Cell. Mol. Neurobiol., 14, 579-588, 1994; Endocrinol., 132, 723-728, 1994; and Neuroendocrinol. 61, 445-452, 1995). For CRF, there are the following two paths: a path by which CRF acts on peripheral immune system or sympathetic nervous system through hypothalamus-pituitary-adrenal system, and a path by which CRF functions as a neurotransmitter in central nervous system (in Corticotropin Releasing Factor: Basic and Clinical Studies of a Neuropeptide, pp. 29-52, 1990). Intraventricular administration of CRF to hypophysectomized rats and normal rats causes an anxiety-like symptom in both types of rats (Pharmacol. Rev., 43, 425-473, 1991; and Brain Res. Rev., 15, 71-100, 1990). That is, there are suggested the participation of CRF in hypothalamus-pituitary-adrenal system and the pathway by which CRF functions as a neurotransmitter in central nervous system.

The review by Owens and Nemeroff in 1991 summarizes diseases in which CRF is

involved (Pharmacol. Rev., 43, 425-474, 1991). That is, CRF is involved in depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastrointestinal diseases, drug dependence, inflammation, immunity-related diseases, etc. It has recently been reported that CRF is involved also in epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, and cephalic external wound (Brain Res. 545, 339-342, 1991; Ann. Neurol. 31, 48-498, 1992; Dev. Brain Res. 91, 245-251, 1996; and Brain Res. 744, 166-170, 1997). Accordingly, antagonists against CRF receptors are useful as therapeutic agents for the diseases described above.

[PROBLEM(S) TO BE SOLVED BY INVENTION]

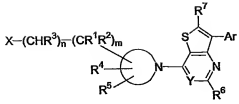
An object of the present invention is to provide an antagonist against CRF receptors which is effective as a therapeutic or prophylactic agent for diseases in which CRF is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastral diseases, drug dependence, epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alpecia, irritable bowel syndrome, sleep disorders, epilepsy, dermatitides, schizophrenia, etc.

[MEANS FOR SOLVING PROBLEM]

The present inventors earnestly investigated thienopyrimidine or thienopyridine derivatives substituted with a cyclic amino group that have a high affinity for CRF receptors, whereby the present invention has been accomplished.

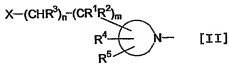
The present invention is thienopyrimidine or thienopyridine derivatives substituted with a cyclic amino group explained below.

A thienopyrimidine or thienopyridine derivative substituted with a cyclic amino group represented by the following formula [I]:



[I]

(wherein the cyclic amino group is represented by the following formula [II]:



[II]

in which the cyclic amino group is a 3- to 8-membered saturated cyclic amine or a 3- to 8-membered saturated cyclic amine bridged with C_{1-5}alkylene or C_{1-4}alkylene-O-C_{1-4}alkylene between any different two carbon atoms of the cyclic amine, which cyclic amine is substituted with a group represented by $-(CR^1R^2)_m-(CHR^3)_n-X$, R^4 and R^5 independently on the same or different carbon atoms of the cyclic amine;

X is cyano or hydroxy;

Y is N or CH;

R^1 is hydrogen, hydroxy, C_{1-5}alkyl, C_{1-5}alkoxy-C_{1-5}alkyl or hydroxy-C_{1-5}alkyl;

R^2 is hydrogen or C_{1-5}alkyl;

R^3 is hydrogen, cyano, C_{1-5}alkyl, C_{1-5}alkoxy-C_{1-5}alkyl or hydroxy-C_{1-5}alkyl;

m is an integer selected from 0, 1, 2, 3, 4 and 5;

n is 0 or 1;

R^4 is hydrogen, hydroxy, hydroxy-C_{1-5}alkyl, cyano, cyano-C_{1-5}alkyl or C_{1-5}alkyl;

R^5 is hydrogen or C_{1-5}alkyl;

R^6 is hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-5}alkyl, hydroxy, C_{1-5}alkoxy, C_{3-8}cycloalkyloxy or $-N(R^8)R^9$;

R^7 is hydrogen, halogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-5}alkyl, hydroxy, C_{1-5}alkoxy, C_{3-8}cycloalkyloxy, $-N(R^{10})R^{11}$, $-CO_2R^{12}$, cyano, nitro, C_{1-5}alkylthio, trifluoromethyl or trifluoromethoxy;

Ar is aryl or heteroaryl which aryl or heteroaryl is unsubstituted or substituted with 1 or more substituents, which are the same or different, selected from the group consisting of halogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-5}alkoxy, C_{1-5}alkylthio, cyano, trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoromethoxy, methylenedioxy, ethylenedioxy and $-N(R^{13})R^{14}$;

R^8 and R^9 are the same or different, and independently are hydrogen or C_{1-5}alkyl;

R^{10} and R^{11} are the same or different, and independently are hydrogen or C_{1-5}alkyl;

R^{12} is hydrogen or C_{1-5}alkyl;

R^{13} and R^{14} are the same or different, and independently are hydrogen or C_{1-5}alkyl)

, individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

The terms used in the present specification have the following meanings.

The term "a 3- to 8-membered saturated cyclic amine" means aziridine, azetidine, pyrrolidine, piperidine, azepane or azocane.

The term "C_{1-5}alkylene" means a straight or branched chain alkylene of 1 to 5 carbon atoms, such as methylene, ethylene, propylene, trimethylene, tetramethylene, pentamethylene or the like.

The term "a 3- to 8-membered saturated cyclic amine bridged with C_{1-5}alkylene or C_{1-4}alkylene-O-C_{1-4}alkylene between any different two carbon atoms of the cyclic amine" includes, for example, 8-azabicyclo[3.2.1]oct-8-yl, 9-azabicyclo[3.3.1]non-9-yl, 7-azabicyclo[2.2.1]hept-7-yl, 3-oxa-7-azabicyclo[3.3.1]non-7-yl and 3-oxa-9-azabicyclo[3.3.1]non-9-yl.

The term "C_{1-5}alkyl" means a straight chain or branched chain alkyl group of 1 to 5 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *t*-butyl, *sec*-butyl, pentyl, isopentyl or the like.

The term "C_{1-5}alkoxy" means a straight chain or branched chain alkoxy group of 1 to 5 carbon atoms, such as methoxy, ethoxy, propoxy, isopropyloxy, butoxy, isobutyloxy, pentyloxy, isopentyloxy or the like.

The term "C_{1-5}alkoxy-C_{1-5}alkyl" means a substituted C_{1-5}alkyl group having the above-

mentioned C_{1-5}alkoxy group as the substituent, such as methoxymethyl, 2-methoxyethyl, 2-ethoxyethyl or the like.

The term "hydroxy-C_{1-5}alkyl" means a substituted C_{1-5}alkyl group having hydroxy group, such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, 4-hydroxybutyl, 5-hydroxypentyl or the like.

The term "cyano-C_{1-5}alkyl" means a substituted C_{1-5}alkyl group having cyano group, such as cyanomethyl, 1-cyanoethyl, 2-cyanoethyl, 3-cyanopropyl, 4-cyanobutyl, 5-cyanopentyl or the like.

The term "C_{3-8}cycloalkyl" means a cyclic alkyl group of 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like.

The term "C_{3-8}cycloalkyl-C_{1-5}alkyl" means a substituted C_{1-5}alkyl group having the above-mentioned C_{3-8}cycloalkyl as the substituent, such as cyclopropylmethyl, cyclopropylethyl, cyclopentylethyl or the like.

The term "C_{3-8}cycloalkyloxy" means a cyclic alkoxy group of 3 to 8 carbon atoms, such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy or the like.

The term "halogen" means fluorine, chlorine, bromine or iodine atom.

The term "C_{1-5}alkylthio" means a straight chain or branched chain alkylthio group of 1 to 5 carbon atoms, such as methylthio, ethylthio, propylthio or the like.

The term "aryl" means a monocyclic or bicyclic group of 6 to 12 ring carbon atoms having at least one aromatic ring, such as phenyl, naphthyl, or the like.

The term "heteroaryl" means a monocyclic or bicyclic group of 5 to 12 ring atoms having at least one aromatic ring having in its ring 1 to 4 atoms which may be the same or different and are selected from nitrogen, oxygen and sulfur, such as pyridyl, pyrimidinyl, imidazolyl, quinolyl, indolyl, benzofuranyl, quinoxalinyl, benzo[1,2,5]thiadiazolyl, benzo[1,2,5]oxadiazolyl or the like.

The term "C_{2-5}alkenyl" means a straight chain or branched chain alkenyl group of 2 to 5 carbon atoms, such as vinyl, isopropenyl, allyl or the like.

The term "C_{2-5}alkynyl" means a straight chain or branched chain alkynyl group of 2 to 5

carbon atoms, such as ethynyl, prop-1-ynyl, prop-2-ynyl or the like.

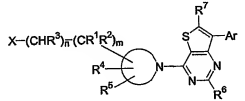
The phrase "aryl or heteroaryl which aryl or heteroaryl is unsubstituted or substituted with 1 or more substituents, which are the same or different, selected from the group consisting of halogen, $C_{1\text{-}5}$alkyl, $C_{3\text{-}8}$cycloalkyl, $C_{2\text{-}5}$alkenyl, $C_{2\text{-}5}$alkynyl, $C_{1\text{-}5}$alkoxy, $C_{1\text{-}5}$alkylthio, cyano, trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoromethoxy, methylenedioxy, ethylenedioxy and -$N(R^{13})R^{14}$' includes, for example, 2,4-dimethylphenyl, 2,6-dimethylphenyl, 2,4-dibromophenyl, 2-bromo-4-isoproylphenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 2-chloro-4-trifluoromethylphenyl, 4-methoxy-2-methylphenyl, 2-chloro-4-trifluoromethoxyphenyl, 4-isopropyl-2-methylthiophenyl, 2,4,6-trimethylphenyl, 4-bromo-2,6-dimethylphenyl, 4-bromo-2,6-diethylphenyl, 4-chloro-2,6-dimethylphenyl, 2,4,6-tribromophenyl, 2,4,5-tribromophenyl, 2,4,6-trichlorophenyl, 2,4,5-trichlorophenyl, 4-bromo–2,6-dichlorophenyl, 6-chloro-2,4-dibromophenyl, 2,4-dibromo-6-fluorophenyl, 2,4-dibromo-6-methylphenyl, 2,4-dibromo-6-methoxyphenyl, 2,4-dibromo-6-methylthiophenyl, 2,6-dibromo-4-isopropylphenyl, 2,6-dibromo-4-trifluoromethylphenyl, 2-bromo-4-trifluoromethylphenyl, 4-bromo-2-chlorophenyl, 2-bromo-4-chlorophenyl, 4-bromo-2-methylphenyl, 4-chloro-2-methylphenyl, 2,4-dimethoxyphenyl, 2,6-dimethyl-4-methoxyphenyl, 4-chloro-2,6-dibromophenyl, 4-bromo-2,6-difluorophenyl, 2,6-dichloro-4-trifluoromethylphenyl, 2,6-dichloro-4-trifluoromethoxyphenyl, 2,6-dibromo-4-trifluoromethoxyphenyl, 2-chloro-4,6-dimethylphenyl, 2-bromo-4,6-dimethoxyphenyl, 2-bromo-4-isopropyl-6-methoxyphenyl, 2,4-dimethoxy-6-methylphenyl, 2,6-dimethyl-4-[2-(2-hydroxyethylamino)ethoxy]phenyl, 6-dimethylamino-4-methylpyridin-3-yl, 2-chloro-6-trifluoromethylpyridin-3-yl, 2-chloro-6-trifluoromethoxypyridin-3-yl, 2-chloro-6-methoxypyridin-3-yl, 6-methoxy-2-trifluoromethylpyridin-3-yl, 2-chloro-6-difluoromethylpyridin-3-yl, 6-methoxy-2-methylpyridin-3-yl, 2,6-dimethoxypyridin-3-yl, 4,6-dimethyl-2-trifluoromethylpyrimidin-5-yl, 2-dimethylamino-6-methylpyridin-3-yl.

The "pharmaceutically acceptable salts" in the present invention include, for example, salts with an inorganic acid such as sulfuric acid, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid or the like; salts with an organic acid such as acetic acid, oxalic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzenesulfonic acid,

methanesulfonic acid, *p*-toluenesulfonic acid, benzoic acid, camphorsulfonic acid, ethanesulfonic acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, malic acid, malonic acid, mandelic acid, galactaric acid, naphthalene-2-sulfonic acid or the like; salts with one or more metal ions such as lithium ion, sodium ion, potassium ion, calcium ion, magnesium ion, zinc ion, aluminium ion or the like; salts with amines such as ammonia, arginine, lysine, piperazine, choline, diethylamine, 4-phenylcyclohexylamine, 2-aminoethanol, benzathine or the like.

A compound of the present invention includes any isomers such as diastereomers, enantiomers, geometricisomers and tautomeric forms. In a compound represented by formula [I], if the cyclic amino group has one or more chiral carbons and/or if there is an axial chirality between Ar and thienopyrimidine (or thienopyridine) ring, several stereoisomers (diastereomers or enantiomers) can exist. The compound of the present invention includes the individual isomers and the racemic and non-racemic mixtures of the isomers.

Preferable examples of the compound of the present invention are as follows.

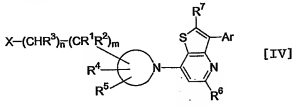


[III]

That is preferable are compounds of the formula [III] in which X, m, n, the cyclic amino group, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and Ar are as defined in claim 1. More preferable are compounds of the formula [III] in which X is cyano; the cyclic amino group is a 4- to 7-membered saturated cyclic amine; n is 0; m is 0 or 1; R^1, R^2, R^4 and R^5 are hydrogen; R^6 is $C_{1\text{-}5}$alkyl; R^7 is hydrogen or $C_{1\text{-}5}$alkyl; and Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen, $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$alkoxy, $C_{1\text{-}3}$alkylthio, trifluoromethyl, trifluoromethoxy and $-N(R^{13})R^{14}$ (wherein R^{13} and R^{14} are the same or different, and independently are hydrogen or $C_{1\text{-}3}$alkyl).

Other preferable are compounds of the formula [III] in which X is hydroxy; the cyclic

amino group is a 4- to 7-membered saturated cyclic amine; n is 0; m is an integer selected from 1,2 and 3; R^1, R^2, R^4 and R^5 are hydrogen; R^6 is C_{1-5}alkyl; R^7 is hydrogen or C_{1-5}alkyl; and Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, trifluoromethyl, trifluoromethoxy and $-N(R^{13})R^{14}$ (wherein R^{13} and R^{14} are the same or different, and independently are hydrogen or C_{1-3}alkyl).



[IV]

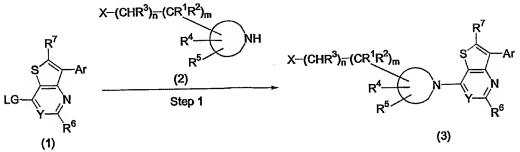
Other preferable are compounds of the formula [IV] in which X, m, n, the cyclic amino group, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and Ar are as defined in claim 1. More preferable are compounds of the formula [IV] in which X is cyano; the cyclic amino group is a 4- to 7-membered saturated cyclic amine; n is 0; m is 0 or 1; R^1, R^2, R^4 and R^5 are hydrogen; R^6 is C_{1-5}alkyl; R^7 is hydrogen or C_{1-5}alkyl; and Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, trifluoromethyl, trifluoromethoxy and $-N(R^{13})R^{14}$ (wherein R^{13} and R^{14} are the same or different, and independently are hydrogen or C_{1-3}alkyl).

Other preferable are compounds of the formula [IV] in which X is hydroxy; the cyclic amino group is a 4- to 7-membered saturated cyclic amine; n is 0; m is an integer selected from 1,2 and 3; R^1, R^2, R^4 and R^5 are hydrogen; R^6 is C_{1-5}alkyl; R^7 is hydrogen or C_{1-5}alkyl; and Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, trifluoromethyl, trifluoromethoxy and $-N(R^{13})R^{14}$ (wherein R^{13} and R^{14} are the same or different, and independently are hydrogen or C_{1-3}alkyl).

The compound of the formula [I] can be produced, for example, by the process shown in the following reaction scheme 1 (in the following reaction scheme, R^1, R^2, R^3, R^4, R^5, R^6, R^7, m, n, X, Y and Ar are as defined above, LG is chloro, bromo, iodo, methanesulfonyloxy,

benzenesulfonyloxy, toluenesulfonyloxy or trifluoromethanesulfonyloxy group).

Reaction Scheme 1



Step 1:

Compound (3), a compound of the present invention, can be obtained by reacting Compound (1) with Compound (2) in an inert solvent in the presence or absence of a base. Herein, the base includes, for example, amines such as triethylamine, *N,N*-diisopropylethylamine, pyridine and the like; inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, potassium hydroxide, barium hydroxide, sodium hydride and the like; metal alcoholates such as sodium methoxide, sodium ethoxide, potassium *tert*-butoxide and the like; metal amides such as sodium amide, lithium diisopropylamide and the like; and Grignard reagents such as methylmagnesium bromide and the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, xylene and the like; amides such as *N,N*-dimethylformamide, *N*-methylpyrrolidone, *N,N*-dimethylacetamide and the like; acetonitrile; dimethyl sulfoxide; pyridine; water; and mixtures of solvents selected from these inert solvents.

The compound of the present invention can be converted to a salt in an inert solvent with an inorganic acid such as sulfuric acid, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid or the like, with an organic acid such as acetic acid, oxalic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzenesulfonic acid, methanesulfonic acid, *p*-

toluenesulfonic acid, benzoic acid, camphorsulfonic acid, ethanesulfonic acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, malic acid, malonic acid, mandelic acid, galactaric acid, naphthalene-2-sulfonic acid or the like, with an inorganic base such as lithium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, zinc hydroxide, aluminium hydroxide or the like or with an organic base such as ammonia, arginine, lysine, piperazine, choline, diethylamine, 4-phenylcyclohexylamine, 2-aminoethanol, benzathine or the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; esters such as ethyl acetate, ethyl formate and the like; ketones such as acetone, methylethylketone and the like; hydrocarbons such as benzene, toluene and the like; amides such as *N,N*-dimethylformamide, *N*-methylpyrrolidone, *N,N*-dimethylacetamide and the like; acetonitrile; dichloromethane; chloroform; dimethyl sulfoxide; pyridine; water; and mixtures of solvents selected from these inert solvents.

The compound of the present invention is useful as a therapeutic or prophylactic agent for diseases in which CRF is considered to be involved. For this purpose, the compound of the present invention can be formulated into tablets, pills, capsules, granules, powders, solutions, emulsions, suspensions, injections and the like by a conventional preparation technique by adding conventional fillers, binders, disintegrators, pH-adjusting agents, solvents, etc.

The compound of the present invention can be administered to an adult patient in a dose of 0.1 to 500 mg per day in one portion or several portions orally or parenterally. The dose can be properly increased or decreased depending on the kind of a disease and the age, body weight and symptom of a patient.

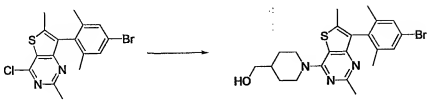
[ENBODIMENTS OF THE INVENTION]

The present invention is concretely explained with reference to the following examples and test example, but is not limited thereto.

Example 1

Synthesis of 2-{1-[7-(4-bromo-2,6-dimethyl-phenyl)-2,6-dimethyl-thieno[3,2-

d]pyrimidin-4-yl]-piperidin-4-yl}-ethanol hydrochloride (compound 1-004)

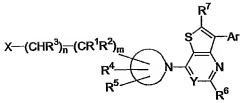


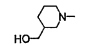
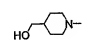
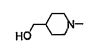
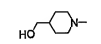
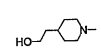
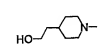
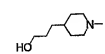
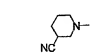
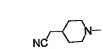
(1) A mixture of 7-(4-bromo-2,6-dimethyl-phenyl)-4-chloro-2,6-dimethyl-thieno[3,2-*d*]pyrimidine (500 mg), piperidin-4-ylmethanol (226 mg), *N*,*N*-diisopropylethylamine (253 mg) in ethanol (1.5 mL) was heated at reflux for 1 day. The reaction mixture was cooled to room temperature, poured into a saturated aqueous sodium hydrogencarbonate, and then extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane/EtOAc = 3 : 1) to obtain 2-{1-[7-(4-bromo-2,6-dimethyl-phenyl)-2,6-dimethyl-thieno[3,2-d]pyrimidin-4-yl]-piperidin-4-yl}-ethanol as a white solid (568 mg).

(2) To a suspension of 2-{1-[7-(4-bromo-2,6-dimethyl-phenyl)-2,5-dimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]-piperidin-4-yl}-ethanol (568 mg) in a mixture (1 : 1) of EtOH and EtOAc (2 mL) was added 4 M HCl in EtOAc (0.37 mL) under ice-cooling. The mixture was stirred overnight to afford a white crystal. The crystal was collected by filtration to give the title compound (532 mg).

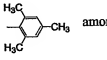
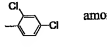
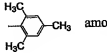
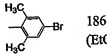
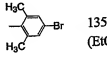
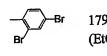
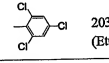
Table 1 lists the compound obtained in Example 1 and compounds obtained by the similar procedure as in Example 1.

Table 1[*1]



Com. No.	Ex. No.	X–(CR²R³)n–(CHR¹)m, R⁴, R⁵, N	Y	R⁶	R⁷	-Ar	melting point (°C) (solvent for crystallization)
1-001	1		N	CH_3	H		amorphous
1-002	1		N	CH_3	H		amorphous
1-003	1		N	CH_3	H		177-180[*2] (EtOAc/EtOH)
1-004	1		N	CH_3	CH_3		242-244[*2] (EtOAc/EtOH)
1-005	1		N	CH_3	H		192-194[*2] (EtOH)
1-006	1		N	CH_3	CH_3		192-193[*2] (EtOAc/EtOH)
1-007	1		N	CH_3	H		amorphous
1-008	1		N	CH_3	H		amorphous
1-009	1		N	CH_3	H		163-165[*2] (EtOAc/EtOH)

1-010	1		N	CH_3	CH_3		202-204*2 (EtOAc/EtOH)
1-011	1		CH	CH_3	H		amorphous
1-012	1		CH	CH_3	H		amorphous
1-013	1		CH	CH_3	H		amorphous
1-014	1		CH	CH_3	H		228-230*2 (EtOAc/EtOH)
1-015	1		CH	CH_3	CH_3		234-236*2 (EtOAc/EtOH)
1-016	1		CH	CH_3	H		196-199*2 (EtOAc/EtOH)
1-017	1		CH	CH_3	H		231-233*2 (EtOAc/EtOH)
1-018	1		CH	CH_3	H		172-174*2 (EtOAc)
1-019	1		CH	CH_3	CH_3		182-184*2 (EtOAc/EtOH)
1-020	1		CH	CH_3	H		166-168*2 (EtOAc/EtOH)
1-021	1		CH	CH_3	H		158-160*2 (EtOAc/EtOH)

1-022	1		CH	CH_3	H		amorphous
1-023	1		CH	CH_3	H		amorphous
1-024	1		CH	CH_3	H		amorphous
1-025	1		CH	CH_3	H		186-188*2 (EtOAc/IPE)
1-026	1		CH	CH_3	CH_3		135-137*2 (EtOAc/EtOH)
1-027	1		CH	CH_3	H		179-182*2 (EtOAc/EtOH)
1-028	1		CH	CH_3	H		203-205*2 (EtOAc)

*1: Com. No. = compound number, Ex. No. = example number, solvent for crystallization; EtOAc = ethyl acetate, EtOH = ethanol, IPE = diisopropylether

Analytical data of non-crystal compounds are described below.

1-001:

MS (Pos, ES): 408 $(M+1)^+$, 410 $(M+3)^+$, 430 $(M+Na)^+$, 432 $(M+Na+2)^+$; NMR (300 MHz, $CDCl_3$) δ 1.50-2.13 (5 H, m), 2.56 (3H, s), 3.48-3.62 (2H, m), 3.71-4.00 (3 H, m), 4.06-4.29 (2 H, m), 7.35 (1 H, dd, J = 2.0, 8.4 Hz), 7.52 (1 H, d, J = 2.0 Hz), 7.57 (1H, d, J = 8.4 Hz), 7.84 (1 H, s)

1-002:

MS (Pos, ES): 408 $(M+1)^+$, 410 $(M+3)^+$; HPLC Retention time: 9.69 (Xterra MS C18 (Waters, Milford, MA) 3.5 μm, 4.6 x 100 mm); Flow rate 1.6 ml/min. Three mobile phases (mobile phase

A 95% 25mM ammonium acetate + 5% acetonitrile; mobile phase B: acetonitrile; mobile phase C: methanol) were employed to run a gradient condition from 100 % A to 50% B and 50% C in 10 min., to 100 % B in 1 min, 100% B for 3 min. and reequilibrate with 100 % A for 2.5 min)

1-007:

MS (Pos, ES): 436 $(M + 1)^+$, 438 $(M + 3)^+$; **HPLC** Retention time: 9.97 (Xterra MS C18 (Waters, Milford, MA) 3.5 μm, 4.6 x 100 mm); Flow rate 1.6 ml/min. Three mobile phases (mobile phase A 95% 25mM ammonium acetate + 5% acetonitrile; mobile phase B: acetonitrile; mobile phase C: methanol) were employed to run a gradient condition from 100 % A to 50% B and 50% C in 10 min., to 100 % B in 1 min, 100% B for 3 min. and reequilibrate with 100 % A for 2.5 min)

1-008:

MS (Pos, ES): 403 $(M + 1)^+$, 405 $(M + 3)^+$; **HPLC** Retention time: 9.94 (Xterra MS C18 (Waters, Milford, MA) 3.5 μm, 4.6 x 100 mm); Flow rate 1.6 ml/min. Three mobile phases (mobile phase A 95% 25mM ammonium acetate + 5% acetonitrile; mobile phase B: acetonitrile; mobile phase C: methanol) were employed to run a gradient condition from 100 % A to 50% B and 50% C in 10 min., to 100 % B in 1 min, 100% B for 3 min. and reequilibrate with 100 % A for 2.5 min)

1-011:

MS (Pos, ES): 407 $(M + 1)^+$, 409 $(M + 3)^+$, 429 $(M + Na)^+$, 431 $(M + Na + 2)^+$; NMR (300 MHz, $CDCl_3$) δ 1.20-2.12 (5 H, m), 2.57 (3H, s), 2.80-3.06 (2H, m), 3.52-4.00 (5 H, m), 6.61 (1 H, s), 7.33 (1 H, dd, $J = 2.0$, 8.4 Hz), 7.51 (1 H, d, $J = 2.0$ Hz), 7.63 (1H, d, $J = 8.4$ Hz), 7.73 (1 H, s)

1-012:

MS (Pos, ES): 407 $(M + 1)^+$, 409 $(M + 3)^+$; **HPLC** Retention time: 10.02 (Xterra MS C18 (Waters, Milford, MA) 3.5 μm, 4.6 x 100 mm); Flow rate 1.6 ml/min. Three mobile phases (mobile phase A 95% 25mM ammonium acetate + 5% acetonitrile; mobile phase B: acetonitrile; mobile phase C: methanol) were employed to run a gradient condition from 100 % A to 50% B

and 50% C in 10 min., to 100 % B in 1 min, 100% B for 3 min. and reequilibrate with 100 % A for 2.5 min)

1-013:

MS (Pos, ES): 381 $(M + 1)^+$; **HPLC** Retention time: 9.22 (Xterra MS C18 (Waters, Milford, MA) 3.5 μm, 4.6 x 100 mm); Flow rate 1.6 ml/min. Three mobile phases (mobile phase A 95% 25mM ammonium acetate + 5% acetonitrile; mobile phase B: acetonitrile; mobile phase C: methanol) were employed to run a gradient condition from 100 % A to 50% B and 50% C in 10 min., to 100 % B in 1 min, 100% B for 3 min. and reequilibrate with 100 % A for 2.5 min)

1-022:

MS (Pos, ES): 409 $(M + 1)^+$; **HPLC** Retention time: 9.89 (Xterra MS C18 (Waters, Milford, MA) 3.5 μm, 4.6 x 100 mm); Flow rate 1.6 ml/min. Three mobile phases (mobile phase A 95% 25mM ammonium acetate + 5% acetonitrile; mobile phase B: acetonitrile; mobile phase C: methanol) were employed to run a gradient condition from 100 % A to 50% B and 50% C in 10 min., to 100 % B in 1 min, 100% B for 3 min. and reequilibrate with 100 % A for 2.5 min)

1-023:

MS (Pos, ES): 402 $(M + 1)^+$, 404 $(M + 3)^+$; **HPLC** Retention time: 6.40 (Xterra MS C18 (Waters, Milford, MA) 3.5 μm, 4.6 x 100 mm); Flow rate 1.6 ml/min. Three mobile phases (mobile phase A 95% 25mM ammonium acetate + 5% acetonitrile; mobile phase B: acetonitrile; mobile phase C: methanol) were employed to run a gradient condition from 100 % A to 50% B and 50% C in 10 min., to 100 % B in 1 min, 100% B for 3 min. and reequilibrate with 100 % A for 2.5 min)

1-024:

MS (Pos, ES): 376 $(M + 1)^+$; **HPLC** Retention time: 6.21 (Xterra MS C18 (Waters, Milford, MA) 3.5 μm, 4.6 x 100 mm); Flow rate 1.6 ml/min. Three mobile phases (mobile phase A 95% 25mM ammonium acetate + 5% acetonitrile; mobile phase B: acetonitrile; mobile phase C:

methanol) were employed to run a gradient condition from 100 % A to 50% B and 50% C in 10 min., to 100 % B in 1 min, 100% B for 3 min. and reequilibrate with 100 % A for 2.5 min)

*2: HCl salt

Test Example [CRF receptor binding test]

Monkey amygdala membranes were used as a receptor preparation.

^{125}I-CRF was used as ^{125}I-labeled ligand.

Binding reaction using the ^{125}I-labeled ligand was carried out by the following method described in The Journal of Neuroscience, 7, 88 (1987).

Preparation of receptor membranes:

Monkey amygdala was homogenized in 50 mM Tris-HCl buffer (pH 7.0) containing 10 mM $MgCl_2$, 2 mM EDTA and centrifuged at 48,000 x g for 20 min, and the precipitate was washed once with Tris-HCl buffer. The washed precipitate was suspended in 50 mM Tris-HCl buffer (pH 7.0) containing 10 mM $MgCl_2$, 2 mM EDTA, 0.1% bovine serum albumin and 100 kallikrein units/ml aprotinin, to obtain a membrane preparation.

CRF receptor binding test:

The membrane preparation (0.3 mg protein/ml), ^{125}I-CRF (0.2 nM) and a test drug were reacted at 25°C for 2 hours. After completion of the reaction, the reaction mixture was filtered by suction through a glass filter (GF/C) treated with 0.3% polyethylene imine, and the glass filter was washed three times with phosphate-buffered saline containing 0.01% Triton X-100. After the washing, the radioactivity of the filter paper was measured in a gamma counter.

The amount of ^{125}I-CRF bound when the reaction was carried out in the presence of 1 μM CRF was taken as the degree of nonspecific binding of ^{125}I-CRF, and the difference between the total degree of ^{125}I-CRF binding and the degree of nonspecific ^{125}I-CRF binding was taken as the degree of specific ^{125}I-CRF binding. An inhibition curve was obtained by reacting a definite concentration (0.2 nM) of ^{125}I-CRF with various concentrations of each test drug under the conditions described above. A concentration of the test drug at which binding of ^{125}I-CRF is inhibited by 50% (IC_{50}) was determined from the inhibition curve.

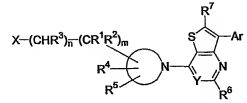
As a result, it was found that compounds 1-003, 1-004, 1-006, 1-010, 1-012, 1-013, 1-014, 1-015, 1-016, 1-017, 1-018, 1-019, 1-020, 1-021, 1-024, 1-025, 1-026, 1-027 and 1-028 can be exemplified as typical compounds having an IC_{50} value of 100 nM or less.

[EFFECT OF THE INVENTION]

According to the present invention, compounds having a high affinity for CRF receptors have been provided. These compounds are effective against diseases in which CRF is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastral diseases, drug dependence, epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alpecia, irritable bowel syndrome, sleep disorders, epilepsy, dermatitides, schizophrenia, etc.

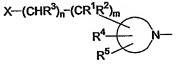
WHAT IS CLAIMED IS:

1. A thienopyrimidine or thienopyridine derivative substituted with a cyclic amino group represented by the following formula [I]:



[I]

(wherein the cyclic amino group is represented by the following formula [II]:



[II]

in which the cyclic amino group is a 3- to 8-membered saturated cyclic amine or a 3- to 8-membered saturated cyclic amine bridged with C_{1-5}alkylene or C_{1-4}alkylene-O-C_{1-4}alkylene between any different two carbon atoms of the cyclic amine, which cyclic amine is substituted with a group represented by $-(CR^1R^2)_m-(CHR^3)_n-X$, R^4 and R^5 independently on the same or different carbon atoms of the cyclic amine;

X is cyano or hydroxy;

Y is N or CH;

R^1 is hydrogen, hydroxy, C_{1-5}alkyl, C_{1-5}alkoxy-C_{1-5}alkyl or hydroxy-C_{1-5}alkyl;

R^2 is hydrogen or C_{1-5}alkyl;

R^3 is hydrogen, cyano, C_{1-5}alkyl, C_{1-5}alkoxy-C_{1-5}alkyl or hydroxy-C_{1-5}alkyl;

m is an integer selected from 0, 1, 2, 3, 4 and 5;

n is 0 or 1;

R^4 is hydrogen, hydroxy, hydroxy-C_{1-5}alkyl, cyano, cyano-C_{1-5}alkyl or C_{1-5}alkyl;

R^5 is hydrogen or C_{1-5}alkyl;

R^6 is hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-5}alkyl, hydroxy, C_{1-5}alkoxy, C_{3-8}cycloalkyloxy or $-N(R^8)R^9$;

R^7 is hydrogen, halogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-5}alkyl, hydroxy, C_{1-}

$_5$alkoxy, C_{3-8}cycloalkyloxy, $-N(R^{10})R^{11}$, $-CO_2R^{12}$, cyano, nitro, C_{1-5}alkylthio, trifluoromethyl or trifluoromethoxy;

Ar is aryl or heteroaryl which aryl or heteroaryl is unsubstituted or substituted with 1 or more substituents, which are the same or different, selected from the group consisting of halogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-5}alkoxy, C_{1-5}alkylthio, cyano, trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoromethoxy, methylenedioxy, ethylenedioxy and $-N(R^{13})R^{14}$;

R^8 and R^9 are the same or different, and independently are hydrogen or C_{1-5}alkyl;

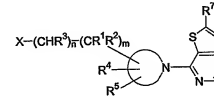
R^{10} and R^{11} are the same or different, and independently are hydrogen or C_{1-5}alkyl;

R^{12} is hydrogen or C_{1-5}alkyl;

R^{13} and R^{14} are the same or different, and independently are hydrogen or C_{1-5}alkyl)

, individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

2. The thienopyrimidine derivative substituted with the cyclic amino group according to claim 1 represented by the following formula [III]:



[III]

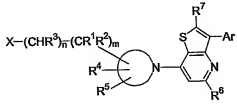
(wherein X, m, n, the cyclic amino group, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and Ar are as defined in claim 1), individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

3. The thienopyrimidine derivative substituted with the cyclic amino group according to claim 2 represented by formula [III], wherein X is cyano; the cyclic amino group is a 4- to 7-membered saturated cyclic amine; n is 0; m is 0 or 1; R^1, R^2, R^4 and R^5 are hydrogen; R^6 is C_{1-}

$_5$alkyl; R^7 is hydrogen or C_{1-5}alkyl; and Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, trifluoromethyl, trifluoromethoxy and $-N(R^{13})R^{14}$ (wherein R^{13} and R^{14} are the same or different, and independently are hydrogen or C_{1-3}alkyl), individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

4. The thienopyrimidine derivative substituted with the cyclic amino group according to claim 2 represented by formula [III], wherein X is hydroxy; the cyclic amino group is a 4- to 7-membered saturated cyclic amine; n is 0; m is an integer selected from 1, 2 and 3; R^1, R^2, R^4 and R^5 are hydrogen; R^6 is C_{1-5}alkyl; R^7 is hydrogen or C_{1-5}alkyl; and Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, trifluoromethyl, trifluoromethoxy and $-N(R^{13})R^{14}$ (wherein R^{13} and R^{14} are the same or different, and independently are hydrogen or C_{1-3}alkyl), individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

5. The thienopyridine derivative substituted with the cyclic amino group according to claim 1 represented by the following formula [IV]:



[IV]

(wherein X, m, n, the cyclic amino group, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and Ar are as defined in claim 1), individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

6. The thienopyridine derivative substituted with the cyclic amino group according to claim 5 represented by formula [IV], wherein X is cyano; the cyclic amino group is a 4- to 7-membered saturated cyclic amine; n is 0; m is 0 or 1; R^1, R^2, R^4 and R^5 are hydrogen; R^6 is $C_{1\text{-}5}$alkyl; R^7 is hydrogen or $C_{1\text{-}5}$alkyl; and Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen, $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$alkoxy, $C_{1\text{-}3}$alkylthio, trifluoromethyl, trifluoromethoxy and $-N(R^{13})R^{14}$ (wherein R^{13} and R^{14} are the same or different, and independently are hydrogen or $C_{1\text{-}3}$alkyl), individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

7. The thienopyridine derivative substituted with the cyclic amino group according to claim 5 represented by formula [IV], wherein X is hydroxy; the cyclic amino group is a 4- to 7-membered saturated cyclic amine; n is 0; m is an integer selected from 1, 2 and 3; R^1, R^2, R^4 and R^5 are hydrogen; R^6 is $C_{1\text{-}5}$alkyl; R^7 is hydrogen or $C_{1\text{-}5}$alkyl; and Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen, $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$alkoxy, $C_{1\text{-}3}$alkylthio, trifluoromethyl, trifluoromethoxy and $-N(R^{13})R^{14}$ (wherein R^{13} and R^{14} are the same or different, and independently are hydrogen or $C_{1\text{-}3}$alkyl), individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

8. An antagonist for CRF receptors, comprising a thienopyrimidine or thienopyridine derivative substituted with a cyclic amino group, a pharmaceutically acceptable salt thereof or its hydrate according to any one of claims 1 to 7, as an active ingredient.

9. Use of a thienopyrimidine or thienopyridine derivative substituted with a cyclic amino group, a pharmaceutically acceptable salt thereof or its hydrate according to any one of claim 1 to 7, for the manufacture of an antagonist for CRF receptors.

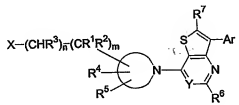
[ABSTRACT]

[PROBLEM TO BE SOLVED]

An object of the present invention is to provide an antagonist against CRF receptors which is effective as a therapeutic or prophylactic agent for diseases in which CRF is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastral diseases, drug dependence, epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alpecia, irritable bowel syndrome, sleep disorders, epilepsy, dermatitides, schizophrenia, etc.

[SOLUTION]

A thienopyrimidine or thienopyridine derivative substituted with a cyclic amino group represented by the following formula [I]:



[I]

has a high affinity for CRF receptors and is effective against diseases in which CRF is considered to be involved.

特願２００４－００１３１０

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識別番号 [０００００２８１９]

1．変更年月日 １９９０年 ８月２２日
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